the amendments to the claims and the remarks presented herein.

The claims in the application are claims 17 to 48, all other claims having been cancelled. Applicants are submitting a copy of PTO Form-2038 to cover the $216.00 additional filing fee for having twelve claims in excess of 20.

It is believed that the new claims are free of the Examiner's objections, 112 rejections and the 101 rejection. The claims have been limited to an isolated polypeptide as suggested by the Examiner where appropriate and are believed to be based upon an enabling disclosure. The Examiner's suggestions with respect to 112, second paragraph, rejections, have been adopted and therefore, the present claims comply with 35 USC 112.

Claim 1 was rejected under 35 USC 103 as being obvious over the Celeste et al patent taken in view of the Ben-Basset et al and Hirel references and claims 1 and 2 were rejected as being obvious over the same references taken in further view of the Hotten et al and Cerletti et al references. Claims 1 to 7 and 11 to 15 were rejected as being obvious over the said prior art mentioned above taken in further view of the Neidhardt et al, Adams et al and Ethridge references. The Examiner indicated that SEQ ID No: 4 was free of the prior art of record.

Applicants respectfully traverse these grounds of rejection

since the combination of the prior art does not render obvious Applicants' invention. If one combined the Hirel, Ben-Bassat et al, Celeste et al, Hotten et al and Cerletti references as the Examiner has done with the benefit of Applicants' disclosure, one would yield MP52 starting with Pro (119) amino acids, at a small percentage at the most (6.5% according to Hirel in the paragraph cited by the Examiner) but always in admixture with mature MP52 starring with Ala (120 amino acid) and mature MP 52 with an additional Met at the N-terminus (121 amino acids). The inventors of the present application have actually found that 120 (Ala-Pro residue) and 121 (Met-Ala-Pro residue) as well as the 119 (Pro residue) amino acid proteins. The cited art however does not discuss how MP52 starting with Pro (119 amino acids) and mature MP52 (Ala-Pro residue, 120 amino acids) could be obtained from the mixture in purer form. 100% separation is practically impossible on a large scale by common protein purification methods because the three proteins differ only by one or two amino acids at the N-terminus as pointed out in the last sentence on page 2 of the application wherein it is stated "It was extremely difficult to isolate pure MP52 at least with a mature region from the mixture."

Moreover, when expressing three different forms, of which only one is further used, the yield would be much smaller. The prior art does not suggest how to obtain sufficient amounts of pure MP52 starting with Pro. The cited documents do not suggest how to obtain pure mature MP52 starting only with Ala from prokaryotes or

cukaryotes since the separation of mature MP52 from the precursor in eukaryotes proceeds according to the RXXR rule (as in the case of TGF-ß-proteins). Also some MP52 having an additional Arg at the N-terminus (121 amino acids) is found besides mature MP52 starting with Ala (120 amino acids). It was found by the inventors upon expressing MP52 in CHO cells (commonly used cells for expressing BMPs). Thus, it is difficult to obtain pure MP52 starting with only one in the same amino acids at the N-terminus. In order to be used a pharmaceutical product for humans however, it is most favorable to reproducibly manufacture a well characterized protein having a defined N-terminus and this is only possible by the claimed expression of Pro-MP52 (SEQ ID No: 1) in E.coli.

In response to the Examiner's argument that this is an obvious step, it must be stated that it is not a matter of course that in the case of an over produced protein in E.coli, sufficient methionine is split off so that an undesired mixture of proteins with and without methionine may result in that case as well (see Table 1 of Hirel, where only 88.2% of Met are split off when starting with prolin) (as opposed to 95.8% in the case of Ala). The inventors have shown however that surprisingly, a high processing rate is achieved in the case of Pro-MP52 as can be seen by the last paragraph of Example 3 wherein it is stated "The protein of the invention comprises 119 amino acid residues starting from the N-terminus Pro singly." Thus, Pro-MP52 is particularly valuable for use in humans because its activity does not differ

from that of mature MP52. While it can be assumed that activity remains, it has not been clear whether the same activity is preserved or only a reduced activity which is no longer of interest economically speaking.

In connection with the activity of shortened forms of MP52, Celeste et al talks about "expected" activity but there is no pertinent showing thereof. In the case of Pro-MP52 compared with Ala-Pro-MP52 one can only speculate as to whether the identical activity can be furnished in the end and it can only be shown by practical experiments. Celeste et al does not show any practical experiments concerning shortened forms and Celeste et al only finds MP52 activity in the tendon/ligament area and even contends that MP52 does not show any cartilage/bone-inducing activity in his experiments. Example 4 of the reference uses the Rosen-modified Sampath-Reddi assay which typical for detecting cartilage and bone inducing activity. Cartilage and bone are found in the case of BMP-2 but not in the case of BMP-12 where only "embryonic tendon"is formed.

In Example 6 of the reference, it is stated that MP52 shows results comparable to BMP-12 i.e. concluding that MP52 has no cartilage/bone-inducing activity in the process of Celeste et al although, there is no actual data shown. Cartilage/bone-inducing activity of MP52 however has already been shown in various assays as well as in the present application. Thus, the statements on

MP52 activity in the Celeste et al patent at least, cannot be applied to activities in the cartilage/bone area because according to Celeste et al, MP52 has no activity at al there. Therefore, starting out from the statements in the Celeste et al patent, one can at best speculate on activities but there is no enablement in said patent. The skilled artisan could not take any clear teaching therefrom as to where or what can be changed in the N-terminus region to find comparable cartilage/bone-inducing activities of MP52. Therefore, the various combination of references does not anticipate or render obvious Applicants' invention and withdrawal of these grounds of rejection is requested.

In view of the amendments to the claims and the above remarks, it is believed that the claims clearly point out Applicants' patentable distinction from the prior art. Therefore, favorable consideration of the application is requested.

Respectfully submitted,
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CAM:ds
Enclosures